Familial gastric cancer

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ORIGINAL ARTICLE

Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance

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Abstract Hereditary diffuse gastric cancer (HDGC) is a relatively rare disorder, with a mutated *CDH1* gene as the only known cause. Carriers of a germline mutation in *CDH1* have a lifetime risk of >80% of developing diffuse gastric cancer. As periodic gastric surveillance is of limited value in detecting early stages of HDGC, prophylactic gastrectomy is advised for this patient group. Little is known about other types of familial gastric cancer. The Dutch working group on hereditary gastric cancer has formulated guidelines for various aspects of medical management for families and individuals at high risk of developing gastric cancer, including criteria for referral, classification, diagnostics, and periodic gastric surveillance. These guidelines are not limited to HDGC and are therefore partially complementary to the guidelines on hereditary diffuse gastric cancer of the international gastric cancer linkage consortium (IGCLC 2010). In order to optimize the care and increase the knowledge on hereditary gastric cancer it is important to centralize medical care for these patients. National and international collaboration is warranted to improve the quality of research by increasing the size of study cohorts.

Keywords Familial gastric cancer · Hereditary diffuse gastric cancer · CDH1 · Gastric surveillance · Prophylactic gastrectomy · Intestinal gastric cancer

This study is conducted on behalf of the Dutch Working Group on Hereditary Gastric Cancer

Please refer the Appendix section for Dutch Working Group on Hereditary Gastric Cancer group members

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Introduction

Gastric cancer belongs to the most frequent cancer related death causes worldwide [1], with a 5-year survival of 20%. The mean age at diagnosis is above age 60. Only 6–7% of gastric cancers present before age 50 and <2% before age 40. The incidence of gastric cancer varies widely from 4 to 10 per 100.000 in North America, Africa, South Asia and Oceania to 69 per 100.000 in North-East Asia [2], with rates in between these in Europe and South America.

Causes of gastric cancer

Environmental and inherited factors

The etiology of gastric cancer is multifactorial, with a role for both genetic and exogenic factors. The main exogenic factors are *Helicobacter pylori* infection, diet and smoking [3–5]. The strong decrease in incidence in the last decennia [6] is one of the indications that exogenic factors play an important role in gastric cancer development.

Gastric cancer is usually sub typed as an intestinal type and a diffuse type [7]. Mixed types have been reported as well. Diffuse gastric cancer often contains signet ring cells and is then indicated as signet ring cell carcinoma (Fig. 1). Especially the incidence of the distal, intestinal type of gastric cancer has decreased (Fig. 2). This is partially caused by the decrease of *H. pylori* prevalence in the Western population. The relationship between *H. pylori* and the diffuse type of gastric cancer is less clear. For this type of gastric cancer, no other exogenic risk factors are known and its incidence has not decreased which suggests that genetic factors play a more important role in diffuse gastric cancer [7, 8].

Approximately 5% of gastric cancers is caused by an autosomal dominant inherited trait, with carriers having a strongly increased risk of developing gastric cancer and probably of other types of cancer. Indications for inherited gastric cancer are: (a) a young age at diagnosis, (b) familial clustering of gastric cancer, and (c) gastric cancer and the presence of a second primary cancer in the same patient. In families with clustering of gastric cancer cases, the diffuse type is the most frequent, but not the only, presenting histological type. Familial occurrence of intestinal gastric cancer is rare, but several cases have been reported [9–11].

Diffuse gastric cancer caused by germline mutations in the CDH1 gene

Heterozygous inactivating germline mutations in *CDH1* are found in about 30% of families fulfilling the diagnostic criteria for hereditary diffuse gastric cancer (HDGC) as established by the international gastric cancer linkage consortium (IGCLC) [12–14]. *CDH1* encodes the protein E-cadherin, which plays an important role in cell–cell adhesion and the maintenance of epithelial integrity. Loss of E-cadherin leads to the typical phenotype of diffuse gastric cancer, which initially spreads within the mucosa only and at a later stage invades the gastric wall [15, 16].

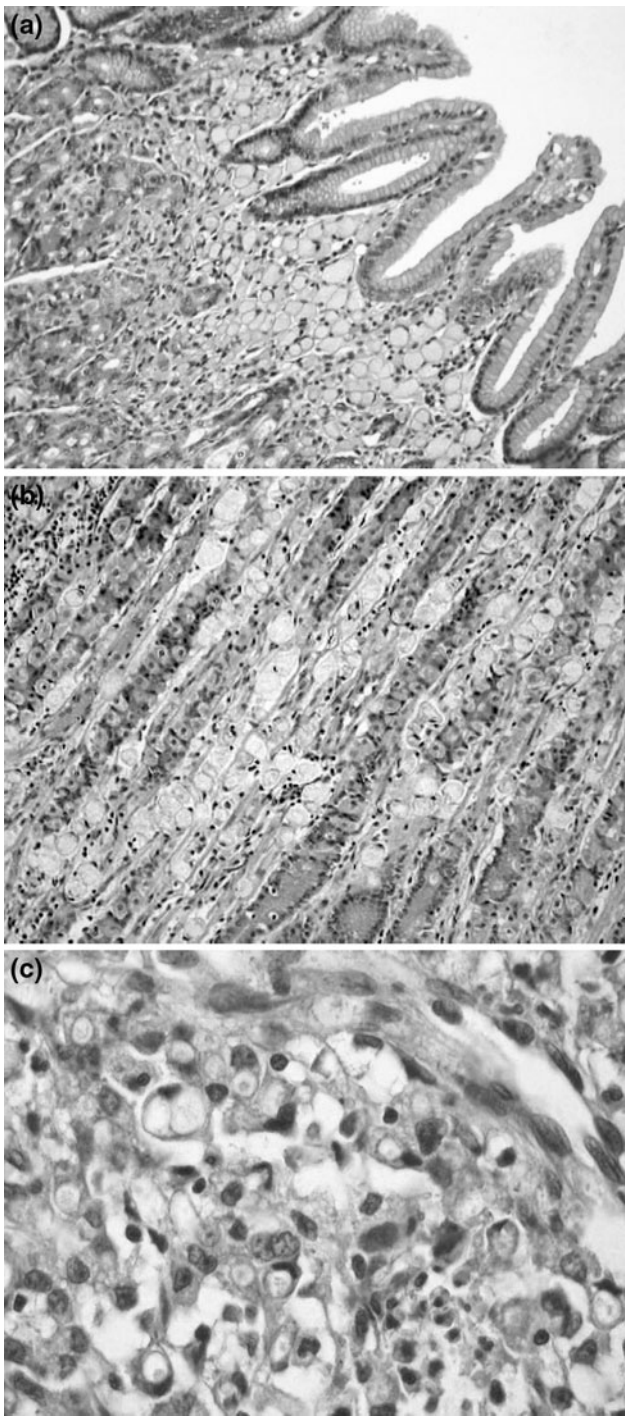

Fig. 1 a Intramucosal signet ring cell carcinoma, b intra-epithelial signet ring cells, c invasive signet ring cell carcinoma

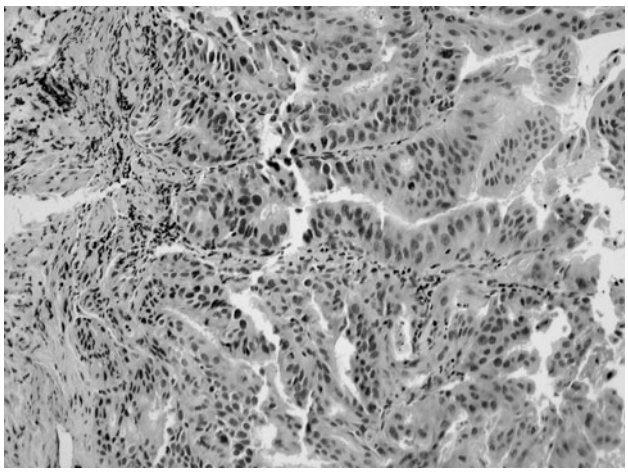

Fig. 2 intestinal type gastric carcinoma

In HDGC caused by germline mutations in *CDH1*, the lifetime risk of developing gastric cancer is supposed to be higher than 80% and the mean age at diagnosis of gastric cancer is as young as 40 years of age, with a range from younger than 20 to older than 70. This large variation in age at diagnosis is seen even within families [17]. Female carriers have an additional high risk of developing lobular breast cancer (LBC) with a lifetime risk of 60% by the age of 80 years, rising from age 40 [12]. Worldwide, about 100 *CDH1* mutation positive families have been reported [14]. Because of the high risk of developing gastric cancer and the limited value of surveillance for high-risk lesions, prophylactic gastrectomy is advised to mutation carriers in these families [12, 18]. Despite the small proportion of gastric cancer patients that originate from HDGC families, identification of these families is important in order to initiate preventive measures in these high risk individuals.

Other familial gastric cancer types and hereditary tumour syndromes

In the majority of families meeting the diagnostic criteria for HDGC syndrome, no causal gene defect is known. In most families with intestinal or mixed types of gastric cancer, or those with unknown subtypes due to lack of pathological information on those tumors, a genetic cause cannot be identified as well. In these families, unknown gastric cancer genes are likely to play a role in gastric tumorigenesis. In the absence of an identified germline cancer predisposing mutation prophylactic gastrectomy is not advised to asymptomatic relatives.

In addition to site-specific familial gastric cancer, an increased risk of developing gastric cancer is known in several other hereditary tumour syndromes: hereditary breast and ovarian cancer (HBOC) [19, 20], Lynch syndrome [21], familial adenomatous polyposis (FAP) [22, 23], MUTYH-associated adenomatous polyposis (MAP) [24], Peutz-Jeghers syndrome [25], juvenile polyposis syndrome [26], Li-Fraumeni syndrome [27] and Cowden syndrome [28]. The incidence of gastric cancer differs between these syndromes, but is generally low. However, in a subset of families with these syndromes, a striking clustering of gastric cancer cases has been observed [19, 21, 27].

Diagnostic work-up and preventive measures: criteria

Referral to genetics services and genetic examination

Because little is known about the different types of inherited gastric cancer and its medical management, we initiated the Dutch national working group on hereditary gastric cancer in 2006, with several members also participating in the IGCLC. The main goal of this working group is to share knowledge, to establish standards of care and to initiate collaborative studies in order to improve the quality of medical care of families with hereditary gastric cancer.

Our working group established criteria for the distinguishing aspects of care for patients with hereditary or familial gastric cancer, i.e. referral to genetics services (Table 1), diagnostic classification of families (Table 2), medical care for *CDH1* mutation carriers (Table 3) and surveillance (Table 4). This policy was based on the fact that hereditary gastric cancer is relatively rare and knowledge on this topic is not widespread among medical specialists. For this reason, we advised to centralize the medical care for this patient group in specialized centers and to collect data for research purposes.

Criteria for referral to genetics services

Criteria for referral are described in Table 1. In most cases, little or no histological data of malignancies in a family are known at the time of referral and are therefore not included in the criteria for referral.

Table 1 Criteria for referral to genetics services

Gastric cancer in one family member before age 40, or
Gastric cancer in 2 first/second degree relatives with one diagnosis before age 50, or
Gastric cancer in 3 first/second degree relatives independent of age, or
Gastric cancer and breast cancer in one patient with one diagnosis before age 50, or
Gastric cancer in one patient and breast cancer in one first/second degree relative with one diagnosis before age 50

Table 2 Diagnostic criteria

1. Hereditary diffuse gastric cancer (HDGC)	Proven pathogenic *CDH1* mutation in the family
2. Clinical HDGC	DGC in 2 first/second degree relatives, with at least one diagnosis before 50
	DGC in 3 or more first/second degree relatives independent of age
3. Possible HDGC	GC in 3 or more first/second degree relatives, independent of age, with at least one diffuse type GC
	DGC in one patient before age 40
	DGC and LBC in one patient
	DGC in one patient and LBC in one first/second degree relative
4. Familial intestinal gastric cancer (FIGC)	IGC in 2 or more first/second degree relatives, with at least one diagnosis before age 50
	IGC in 3 or more first/second degree relatives, independent of age
5. Familial gastric cancer (FGC)	GC in 2 or more first/second degree relatives, with at least one diagnosis before age 50
	GC in 3 or more first/second degree relatives, independent of age
6. Gastric cancer in other tumour syndromes	GC in 2 or more mutation carriers in families with:
	Lynch syndrome
	Hereditary breast and ovarian cancer (HBOC)
	Familial adenomatous polyposis (FAP)
	MUTYH-associated polyposis (MAP)
	Peutz-Jeghers syndrome
	Juvenile polyposis
	Cowden syndrome
	Li-Fraumeni syndrome

GC gastric cancer, *(H)DGC* (hereditary) diffuse gastric cancer, *(F)IGC* (familial) intestinal gastric cancer, *LBC* lobular breast cancer

Clinical diagnosis

After pedigree analysis, verification of diagnoses and, if possible, review of the histology, the clinical geneticist will render a clinical diagnosis. This diagnosis is based on histological subtypes of gastric cancer, the number of affected family members and the presence of other types of cancer in a family. Diagnostic criteria are shown in Table 2.

DNA analysis

DNA analysis may assist in confirming the clinical diagnosis. In families with no detected *CDH1* mutation and with presence of breast cancer or colorectal cancer cases, *BRCA1, BRCA2* and/or Lynch syndrome diagnostics can be considered. In rare cases, specific signs of Cowden syndrome, Peutz-Jeghers syndrome or other genetic syndromes, will be the reason for analysis of relevant genes.

If in an affected patient a causal gene mutation is found, healthy relatives can be tested for that mutation and individualized advises can be given based upon their test results. In families with no affected family members alive, an attempt can be made to analyze *CDH1, BRCA1, BRCA2* or other genes in stored tissue specimens of patients or otherwise in DNA from healthy, preferably first-degree, relatives. Lynch syndrome diagnostics preferably starts by analysis of stored tumour specimens, i.e. studies for presence of micro-satellite-instability (MSI) and for immunohistochemical analysis of the mismatch repair proteins *MLH1, MSH2, MSH6 and PMS2*. Even material of deceased relatives can be investigated for presence of Lynch syndrome characteristics.

Recommendations for individuals from *CDH1* mutation positive HDGC families

CDH1 mutation carriers are currently advised to undergo prophylactic total gastrectomy because of their high lifetime risk of developing gastric cancer and the limited value of surveillance modalities (Table 3).

Counselling

Extensive counseling of mutation carriers is important. Specific attention must be paid to the preferred age at which prophylactic gastrectomy will take place, with respect to education, career, and in females future pregnancies and

Table 3 Recommendations for members from HDGC families

Prophylactic gastrectomy	In *CDH1*-mutation carriers from age 18 and guided by ages at onset in the family
Gastric surveillance according 'Cambridge protocol'	In *CDH1*-mutation carriers from age 20, if prophylactic gastrectomy will not (yet) be performed
(see Table 4)	In individuals with 50% chance of carrying a *CDH1*-mutation
	In FDRs of GC patients from clinical HDGC families without a known genetic cause
Breast surveillance (annual MRI-scan and mammography)	In female carriers of a *CDH1*-mutation or with 50% chance of carrying a *CDH1*-mutation, from age 35

FDRs first-degree relatives, *GC* gastric cancer, *HDGC* hereditary diffuse gastric cancer

Table 4 surveillance strategy

HDGC	Cambridge-protocol:
	Hp-testing and eradication
	Annual gastroscopy with 'high definition' endoscope
	Careful inspection of mucosa during 30 min
	Insufflation and desufflation of the stomach
	Biopsy of mucosal abnormalities
	30 random biopsies (6 from each region: antrum, angulus/transitional zone, corpus, fundus, cardia)
Other categories	Gastroduodenoscopy at age 40 (or at an age 5 years younger than youngest diagnosis in a family)
	Hp-testing and eradication
	Gastric surveillance only in research setting

Hp helicobacter pylori

related nutritional issues. The ages at gastric cancer diagnoses in a specific family may be taken into account. However, the extent to which these ages have a predictive value in estimating the ages of future cases in this family is unknown.

Dietary advices

Before a gastrectomy will be carried out, patients will be referred to a dietitian to optimally prepare them for a necessary change in dietary pattern after the operation. This is important to prevent excessive weight loss and nutritional deficiencies.

Preoperative gastric investigation

The IGCLC guidelines advise preoperative gastric examination with biopsies of mucosal abnormalities [12]. We recommend to mention the main goal of this advice, i.e. the need to complete a gastrectomy by an extensive lymphadenectomy in case of preoperatively diagnosed invasive gastric cancer.

Surgical procedure

The surgical procedure consists of a total gastrectomy with Roux-en-Y esophagojejunostomy. The distal margin should be at least 1.0 cm below the pyloric region to ensure resection through duodenal mucosa. Before performing the reconstruction, a frozen section procedure of the proximal margin is warranted to confirm that no gastric cardia mucosa is left behind and allowing direct re resection. This measure, which is relatively easy to perform, is recommended here in addition to the IGCLC guidelines [12], because any residual gastric mucosa may be at risk for present or subsequent (pre)malignant lesions and inspection of the z-line may not in all cases be sufficient to achieve proximal clearance. In our Dutch experience of prophylactic gastrectomies in 29 *CDH1* mutation carriers [17], we observed that three patients had to undergo re-intervention because of incomplete removal of proximal gastric mucosa. Moreover, the presence or absence of signet ring cells and/or residual gastric mucosa in the resection margins was not systematically documented. The majority, but not all of these carriers were operated in specialized centers by experts in this field. Since we cannot guarantee that any mutation carrier will be treated in a high-specialized center and by the most experienced specialists, we at least aim to provide guidelines in order to minimize the change of insufficient care and second interventions.

If no invasive cancer is diagnosed preoperatively, an extensive lymphadenectomy with higher risk of complications [29] is considered to be unnecessary as the metastatic risk of intramucosal carcinomas is exceedingly low.

Pathological investigation

The 'Swiss roll' technique is the designated pathological procedure to find and localize especially presumed pre-malignant lesions precisely by examining the complete mucosa [30]. Alternative techniques using extensive sampling are also possible (IGCLG) [12]. The pathology report should mention all gastric abnormalities and their localizations, including infiltrating adenocarcinoma components and various presumed pre-malignant lesions (intramucosal and intra-epithelial signet ring cells) as well as the presence of intestinal metaplasia, intestinal-type dysplasia and the presence of signs of *Helicobacter pylori* gastritis. Moreover, histological confirmation of resection margins to consist of duodenal and esophageal mucosa respectively is mandatory as well as reporting any abnormalities.

Follow-up

After the operation, long-term follow-up is warranted to prevent nutritional deficiencies and to detect other late-presenting effects. In all phases of the process, psychosocial support is an integral part of the medical care of this patient group. At this moment, little is known about the psychosocial impact of prophylactic gastrectomies. Data to assess this impact are currently being collected in a cohort of Dutch *CDH1* mutation carriers.

Because of the rarity of the disease, and also the specific requirements for surgical and postsurgical care and for pathological evaluation, we consider it of great importance to centralize the intensive care for HDGC families in specialized centers within multidisciplinary medical teams consisting of a clinical geneticist, gastroenterologist, surgeon, pathologist, psychologist and a dietitian.

Gastric surveillance

Because of the relative low incidence of gastric cancer, gastric surveillance is not routinely part of medical care in Western countries.

In HDGC, the presence of signet ring cells in the gastric mucosa is considered as a precursor stage of diffuse gastric carcinoma, although little is known about its natural course [15, 16]. Longstanding presence of non-proliferative signet ring cells was shown by our group in 2 *CDH1* mutation carriers from one family [17].

Intestinal gastric carcinomas often are preceded by H. pylori induced acute gastritis, which subsequently can progress into chronic gastritis, atrophic gastritis, intestinal metaplasia and dysplasia and in some cases by an intestinal type adenoma [31].

Thus, recognizable precursors are present in at least part of the hereditary gastric cancers. This may lead to an early diagnosis and may ultimately add to an improved prognosis. For this reason, tracing and follow-up of at-risk individuals is highly important. In general, it is not known which premalignant anomalies are to be expected in the various categories of high risk groups.

The 'Cambridge surveillance protocol' (Table 4) is advised for *CDH1* mutation carriers who will not (yet) undergo a prophylactic gastrectomy, to individuals at 50% risk of being carrier who are not (yet) willing to be tested for the mutation as well as for members from HDGC families without a known *CDH1* mutation. Signet ring cells cannot endoscopically be detected, but may be recognized at histological examination of random taken biopsies. However, the risk of sampling error is high. In our series [17], we demonstrated a wide variability of age at onset and aggressiveness of DGC and a longstanding presence of dormant signet ring cells in some patients. The very subtle gastric abnormalities (superficial vacuolozed cells without the typical morphology of signet ring cells) [12, 15] in six of 29 prophylactic removed stomachs were the most consequent, striking and often the only *CDH1*-related alterations, but were not recognized at first pathological examination by experts in this field and only at revision by a second expert. Moreover, the unknown clinical relevance of these lesions and the dormant signet ring cells in some patients emphasizes that the value of gastric surveillance must be placed in perspective.

In regular medicine, only one gastroscopy with biopsies is recommended to first-degree relatives of gastric cancer patients from the other categories of familial gastric cancer (Table 4), in order to diagnose and treat a possible *Helicobacter pylori* colonization and to look for macroscopic mucosal abnormalities that are of clinical relevance. In our opinion, there is no place for gastric follow-up in regular medical care, since very little is known about the value, optimal method and frequency of gastric surveillance. Gastric surveillance should only be carried out in a research setting, in centers with expertise in the field of hereditary gastric cancer.

Conclusions

Hereditary gastric cancer is a rare disease. Besides germline mutations in the *CDH1* gene, few other genetic factors are known, but in the majority of families no genetic cause can be identified. A reliable method for the detection of early stages or precursors of gastric cancer is not yet available. For these reasons, gastric surveillance in high risk families should be performed in specialized centers and preferably within a research setting. The provided criteria for referral to genetics services, for diagnostic classification, for DNA analyses and for surveillance may aid in optimizing medical care for individuals at high risk for developing gastric cancer. The differentiation between subgroups of familial gastric cancer, based on histological and family characteristics, will facilitate research strategies to find yet unknown genetic factors and to detect early stages and precursors of the disease. This requires centralization of medical care for this patient group. Referral of families suspected for hereditary gastric cancer to family cancer centers is important to increase the insight into this disease and to inform at-risk individuals adequately. National and international collaboration in rare diseases as hereditary gastric cancer is warranted to maximize the study cohorts to be investigated.

Appendix

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